# Meningococcal Disease: *Neisseria meningitidis*

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## *NEISSERIA MENINGITIDIS: THE BACTERIUM*

- gram-negative diplococcus
- 13 serogroups based on polysaccharide coat
  - 13 serogroups: A, B, C, D, X, Y, Z, E, W-135, H, I, K, L
  - nine serogroups are known to cause invasive disease (A, B, C1+, C1-, X, Y, W-135, Z and L)
- Groups B and C currently cause the majority of disease in the US (group B causes >50% of cases)
  - Group A occurs most frequently in less developed countries; it is associated with outbreaks and epidemics
  - Group B causes endemic disease (sporadic, isolated cases)
  - Group C is often involved in clusters or outbreaks in both developing and developed countries
  - Group Y can cause sporadic pneumonia and meningitis
  - Group W-135 is increasing in developed countries
- antibiotic resistance has been recognized in Spain, Africa, and Great Britain and is increasing
- fastidious growth conditions required to culture organism
  - blood agar or chocolate agar with increased $CO_2$ for sterile-site samples
  - Thayer-Martin media for samples from sites where competing bacteria are present (T-M media contains inhibitory antibiotics to aid in selection of *N. meningitidis*)

## *HISTORY*

| | |
|---|---|
| **1887:** | *Neisseria meningitidis* was identified as the cause of epidemic meningitis in 1887 by A. Weichselbaum (isolated meningococcus from CSF). |
| **1896/1901:** | "Carrier" state recognized. |
| **1909:** | Bacterial serotypes first recognized. |
| **1920s:** | Recognition that carrier rates in military recruit camps increased during periods of excessive crowding. |
| **1928 -1930, 1941:** | World-wide epidemics of meningitis. |
| **1937:** | Use of sulfonamide therapy provided a simple and effective means of eradicating the carrier state and preventing epidemics. |
| **1963:** | Sulfonamide-resistant *N. meningitidis* recognized during outbreaks in military bases in San Diego, CA. |
| **1970:** | Rifampin adopted as recommended chemoprophylaxis. |
| **1970s:** | Development of vaccines effective against serogroups A and C (bivalent) and A, C, Y, W-135 (quadrivalent). |

## *EPIDEMIOLOGY*

- World-wide distribution of sporadic cases.
    - Meningitis belt extends from sub-Saharan Africa into India/Nepal. Epidemics usually occur every 8 to 12 years in Africa and last 2 to 4 years. Seasonal variations occur in the epidemics, usually corresponding to the dry, hot seasons.
    - In the US, the largest number of cases is usually seen during the winter and early spring (acute respiratory infection [ARI] season)
- The largest percentage of cases is seen among children less than 5 years of age, but a shift in age distribution to those 15 to 19 years of age has been seen in some areas (Washington/Oregon during 1987 to 1992). An increase in cases among those aged 5 through 19 years is also observed during epidemics.
- Epidemics occur most frequently in crowded conditions (i.e., military bases, college settings)
- The incidence of endemic disease peaks in the late winter and early spring

### Invasive Disease:

- Invasive disease upon exposure to an infected person may be dependent upon a combination of host immunologic factors combined with the specific strain of the organism. Highly virulent strains may cause invasive disease in those whose immune systems are compromised either by another illness or by genetic pre-disposition.
    - invasive disease is seen in persons who are newly exposed to the organism (the carrier state is thought to be an immunizing process)
    - a recent history of an upper respiratory infection may play a role in increasing the chance of invasive disease
    - coinfection with a virus or mycoplasma may increase the chance of invasive disease
    - age of the patient, immune status, and integrity of the nasopharyngeal mucosa may be related to the risk of invasion and severe clinical manifestations
    - people with certain chronic conditions appear to be at an increased risk of developing meningococcal disease, i.e., asplenic persons or individuals with deficiencies in the late complement pathway components (C3, C5-C9)

### Carriers:

- Meningococcus is found in the posterior nasopharynx of varying percentages of individuals (carriers) in different populations
    - 5-10% of population in non-endemic areas
    - 17-50% in household contacts (carriage rates in household contacts may be 4 to 5 times greater than the general population)
    - 40-80% in military recruits
    - up to 80 -90% in communities experiencing an outbreak
- The carrier state may be chronic (up to 2 years), intermittent, or transient.
- The duration of the carrier state is variable. In non-epidemic situations, the mean duration of carriage in a U.S. study was 9.6 months, but 38% of those studied were carriers for greater than 16 months.
- Carriage is believed to produce an antibody response and thereby act as an “immunizing experience”.
- Less than 1% of those who are colonized will progress to invasive disease.

**Modes of transmission: respiratory secretions (saliva)**

(1) person-to-person (2) droplet-borne (3) vehicle-borne

- **Incubation period:** 1 to 10 days, most commonly less than 4 days
- **Infectious period:** as long as meningococci are present in nasal/oral secretion; until 24 hours after initiation of effective treatment

## Occurrence of serogroup C in US:

From 1980 to 1993, at least 21 outbreaks of serogroup C occurred throughout the US. Eight of these outbreaks have occurred since 1991. These outbreaks consisted of 10 community-based outbreaks and 11 school-based or institutionally based outbreaks: 8 schools (elementary, junior high, university) and 3 institutions (correctional facilities, job corp). The age distribution of cases associated with outbreaks differs from the age distribution for sporadic cases. Approximately 50% of the community outbreak-associated cases were between 10 to 24 years of age, compared to only 19% of sporadic cases. Persons over 35 years of age accounted for only 4 to 7% of outbreak cases but 23% of sporadic cases. Cases under 2 years of age were similar in both outbreak and sporadic disease.

Subtyping of isolates indicates that five distinct but closely related strains of serogroup C are responsible for most of the outbreaks.

## Occurrence of serogroup Y in US:

From 1989 to 1991, active surveillance for meningococcal illness revealed 2% of cases were caused by serogroup Y. However, by 1995 serogroup Y was reported to account for 21% of cases reported through the National Electronic Telecommunications System for Surveillance by 30 states. Review of cases in Chicago and Connecticut (1991-1996) and active laboratory-based surveillance in California, Atlanta, Tennessee, and Maryland (1989-1995) revealed a similar increase in the number of cases of disease caused by serogroup Y during the indicated time periods. In addition, data indicate that cases of disease caused by serogroup Y were in older individuals than cases caused by non-serogroup Y. Pneumonia was also found to be more common among patients with serogroup Y disease.

| | **Median Case Age** | |
|---|---|---|
| | **Group Y** | **Non-Group Y** |
| **Connecticut** | 29 yrs | 13 yrs |
| **Illinois** | 16 yrs | 2 yrs |
| **Active Lab-Based Surveillance** | 22 yrs | 14 yrs |

From *MMWR*, Serogroup Y meningococcal disease – Illinois, Connecticut and selected areas, United State, 1989-1996, Nov. 22, 1996, vol. 45, no. 46.

## Occurrence of Meningococcal Disease in Massachusetts:

The following table describes surveillance data for reported cases of meningococcal disease from 1994 through 1998:

**Reported Cases of Invasive Meningococcal Disease by Serogroup, 1994-1998**

| | 1994 | 1995 | 1996 | 1997 | 1998 |
|---|---|---|---|---|---|
| Total reported cases | 69 | 51 | 71 | 92 | 55 |
| Group B | 56% | 30% | 23% | 31% | 10% |
| Group C | 25% | 42% | 44% | 34% | 41% |
| Group Y | 17% | 25% | 31% | 32% | 47% |
| Other* | 2% | 3% | 2% | 3% | 2% |

*Other: Groups A, W-135, and Z.

## *CLINICAL MANIFESTATIONS*

Meningococcal infection may be asymptomatic (carrier), cause mild upper respiratory infection symptoms (with fever and mild disease), or cause meningococcemia with multi-organ disease including meningitis. Variations in clinical manifestations are common; and, although symptoms are not age dependent, age may affect the patient's ability to report their symptoms.

- ✓ **Meningitis:** inflammation of the meninges, the membranes surrounding the brain and spinal cord

- ✓ **Meningococcemia:** meningococcal infection of the blood

**Case Fatality:** With early diagnosis, antibiotic therapy and supportive measures, the case fatality rate is less than 10%. In practice, however, the case fatality rate is 10-15%.

## Signs and Symptoms:

### Meningococcal meningitis:

***Diagnostic Triad:*** (1) rapid onset of high fever, (2) stiff neck, and (3) headache. Nausea, vomiting and mental confusion are also commonly seen.
A maculopapular, urticarial or petechial rash may be present. A rash on the palms and soles is sometimes seen and, if present, is pathognomonic for *N. meningitidis* infection. Symptoms evolve rapidly. Immediate intravenous antibiotic therapy is necessary.

### Meningococcemia:

Abrupt onset of fever, chills, malaise, prostration and rash (urticarial, maculopapular, or petechial). Fulminant cases present with purpura, disseminated intravascular coagulation, shock, and/or coma and may lead to death within hours despite appropriate therapy.

**Note:** If symptom onset occurs over an extended period of time (≥7 days), a viral rather than bacterial meningitis should be suspected.

### Rash:

The rash associated with meningococcal disease is usually described as petechial. The petechial rash usually initially appears on the trunk or lower body as discrete lesions 1 to 2 mm in diameter. These lesions can coalesce to form larger ecchymotic lesions (black and blue/purple lesions) called purpura. A transient, nonpruritic, nonpurpuric, maculopapular rash has also been described. The meningococcal rash may occur on the trunk and/or may appear on the volar surfaces of the wrists and forearms, palms, lower legs, ankles and soles. The rash may be misdiagnosed as Rocky Mountain Spotted Fever, rubella, rubeola, or secondary syphilis.

The ability to culture or identify the organism in a gram stain from skin lesion samples is variable.

**Petechial:** tiny reddish or purplish spots containing blood that appear in the skin or mucous membrane

**Purpuric:** patches of purplish discoloration (bruises) resulting from extravasation of blood into skin or mucous membrane

## *TREATMENT*

### Treatment of the Case:

- Standard treatment for cases: intravenous penicillin (penicillin resistance was identified in Spain, Great Britain and Africa during the late 1980s) or second and third generation cephalosporins
- For patients allergic to penicillin: intravenous chloramphenicol
- Duration of treatment varies, but is normally 5 to 7 days

### Chemoprophylaxis of Carriers:

- Note: carrier state chemoprophylaxis is of questionable value
- Sulfonamides were extremely successful in eradicating the carrier state until the 1960s, when resistance appeared
- Penicillin is not effective at eliminating the carrier state
- The current drug of choice is **rifampin** (treatment can result in rifampin resistance in 10 to 27% of those treated). See the section entitled “Control Measures” for alternative antibiotics

# LABORATORY DIAGNOSIS

A confirmed diagnosis involves isolation of *N. meningitidis* from a sterile body fluid (blood, CSF, synovial, pleural, or pericardial fluids).

The Centers for Disease Control and Prevention defines cases of meningococcal illness as follows:

**Confirmed:** A clinically compatible case that is culture confirmed.
**Probable:** A positive antigen test in cerebrospinal fluid or clinical purpura fulminans in the absence of a positive blood culture.
**Laboratory criteria for diagnosis:** Isolation of *Neisseria meningitidis* from a normally sterile site.
**Clinical description:** meningococcal disease presents most commonly as meningitis and/or meningococcemia that may progress rapidly to purpura fulminans, shock and death. However, other manifestations may be observed.

(from Case Definitions for Public Health Surveillance, *MMWR*, Oct. 19, 1990, Vol. 39, No. RR-13.)

## *Laboratory Diagnostic Methods:*

***Bacterial Culture:***

- *N. meningitidis* may be isolated from CSF, blood or other sterile fluids

***Gram Stain:***

- Gram negative diplococci may be found in:
  - blood
  - CSF
  - synovial, pleural, or pericardial fluids
  - smears from petechial skin or mucosal lesions

***CSF:***

- CSF may appear cloudy
- Elevated protein level (caused by increased blood/brain barrier penetration due to cell damage by the bacteria)
- Low glucose level
- WBCs in the CSF with a predominance of polymorphonuclear leukocytes

***Bacterial Antigen Test:***

Counterimmunoelectrophoresis, latex agglutination, and coagglutination have been found to be capable of detecting 0.02 to 0.05 μg of meningococcal capsular antigens per ml of spinal fluid from infected patients. The techniques are rapid and relatively specific, although cross reactions occur (*E. coli* K1) and false-negative results are common. False-negative results may be due to low concentrations of the bacteria in CSF. Bacterial antigens have been detected in urine for longer periods of time than in other body fluids.

***Slide Agglutination:***

This is a rapid analysis that requires pure cultures and reagent antisera. Isolates grown from body fluids may be identified through agglutination and blocking of agglutination with group-specific antisera.

***Polymerase Chain Reaction (PCR):***

PCR has been used to diagnose meningococcal meningitis by examination of CSF. The sensitivity and specificity of the test are both over 90%. PCR may be especially useful in diagnosis when prior antibiotic administration makes culture an ineffective method of diagnosis.

## Why Do Control Measures Need to be Initiated?

Control measures are initiated to prevent the spread of invasive strains to contacts with unknown levels of susceptibility. Attack rates in household contacts of cases have been shown to be 500 to 800 times greater than in the general population. The risk is highest for siblings who share a bedroom. Secondary cases usually occur within 5 days of the primary case, but increased risk for secondary cases can extend for up to 14 days.

## How to Control Transmission to Close Contacts of a Case

Control is implemented through the administration of prophylactic antibiotics to individuals who have been in "close contact" with a case during the 2 weeks prior to onset of symptoms (see below for definition of "close contact"). Preventive treatment of all close contacts should be implemented within the first 2 weeks after onset of symptoms for the case but preferably as soon as possible within the first 24 hours. Contacts of a case should consult their health care provider(s) for prophylaxis options.

When evaluating potential contacts it is important to consider all household contacts, including family members and non-family household members. Evaluation of non-household contacts should include:

**For Children:** contacts in school, daycare, after-school programs, sports teams, baby sitters, close friends, relatives, visitors, parties;

**For Adults:** work contacts, relatives, friends, recreational contacts, parties, visitors, sports teams.

***Prophylactic Antibiotics:*** A health care provider should be consulted for evaluation and appropriate prophylaxis.

Drugs of choice: Rifampin (multiple oral doses; safe for children, do **not** use if pregnant)
**OR**
Ceftriaxone (one intramuscular dose; safe during pregnancy and safe for children)
Efficacy of ceftriaxone only confirmed for group A.
**OR**
Ciprofloxacin (one oral dose; do **not** use if <18 years of age or if pregnant)

**Note:** If the strain is known to be sulfonamide-susceptible, sulfonamide may be used as prophylaxis.

## How to Define a "Close Contact"

"Close contacts" include all household members and those individuals who have had intimate contact with the case's oral secretions (especially saliva), for example through kissing or sharing food or eating or drinking utensils. Also consider sharing lip gloss or cigarettes, sharing of water bottles, sharing of toys among infants and toddlers, shared office space, car pools, and other shared, enclosed spaces.

***Medical personnel:*** prophylaxis is not routinely recommended for medical personnel attending a case except for those who have had intimate exposure to the case (e.g., mouth-to-mouth resuscitation, intubation, or suctioning) prior to the initiation respiratory secretion control measures or before the first 24 hours of antibiotic therapy have been completed by the case.

## *MENINGOCOCCAL VACCINE*

- Two purified polysaccharide vaccines are available against serogroups A and C (bivalent) and against A, C, Y, and W-135 (quadrivalent). No vaccine against group B is presently licensed in the US.

### Who should receive meningococcal vaccine?

- ✓ The vaccines are poorly immunogenic in children less than 2 years of age (the group A component has a fair response in children 3 to 11 months, but the group C component is not effective in inducing an immune response in children less than 2 years of age), therefore the vaccine should not be administered to children less than 2 years of age. (Note: Maternal antibodies will transfer to about 50% of infants at birth. Immunity decreases in early childhood, then increases with age – the carrier state is thought to be an "immunizing process").
- ✓ Routine vaccination of children is not recommended. Vaccination of high-risk children over 2 years of age with quadrivalent vaccine should be considered. High-risk children include children with functional or anatomic asplenia or those with terminal complement component deficiencies.
- ✓ Military recruits receive a single dose of the quadrivalent vaccine upon entry into the US military.
- ✓ Vaccination with the quadrivalent vaccine is recommended for individuals who will be traveling to countries with hyperendemic or epidemic disease, particularly those who will have prolonged contact with the local populace. Travelers should consult their health care provider(s) for more information about vaccination.
- ✓ The vaccine may be indicated for the population-at-risk in the case of a community- or organization-based outbreak (see below).

### Meningococcal Vaccine and the College Student

On October 20, 1999, the Advisory Committee on Immunization Practices (ACIP) modified its recommendations for the use of meningococcal vaccine in college students. The ACIP now recommends that medical care providers of college students provide information to students and their parents about meningococcal disease and the benefits of vaccination. In addition, vaccination should be provided or made easily available to freshman students. Other undergraduate students may also choose to be vaccinated. This change is the result of data collected from on-going studies by the Centers for Disease Control and Prevention, Council of State and Territorial Epidemiologists and the American College Health Association. Preliminary data from these studies suggest that freshman students living in a dormitory setting may be at a moderately higher risk for invasive meningococcal illness.

- Vaccine efficacy is approximately 90% for persons over 5 years of age.
- Protective immune response to the vaccine takes 7 to 14 days after immunization and is protective for 1 to 3 years in those who are vaccinated at $\geq$ 4 years of age (duration of immunity is age-dependent with a shorter duration for younger children than for adults).
- The safety of the vaccine in pregnant women has not been determined; therefore, pregnant women should be immunized only if they have a substantial risk of infection.
- Revaccination after 2 to 3 years may be indicated for individuals at high risk of infection, particularly children who were first immunized under 4 years of age.
- Vaccine is administered subcutaneously as a single 0.5-ml dose.

## Vaccine for use in outbreak settings:

If an institutional or localized community outbreak is identified and the causative organism can be confirmed as serogroup A, C, Y, or W-135, immunization may used for immunoprophylaxis. However, immunization of contacts of sporadic cases is not recommended because the overall risk of infection is low and most of the secondary cases occur within less than 6 days of the initial case (an immune response from vaccination requires 7 to 14 days).

A cost-effectiveness study undertaken by the CDC concluded that routine vaccination of college students was not a cost-effective method of preventing disease in the college population.

## The evaluation and management of outbreaks of meningococcal disease:

Although the benefit of vaccination for control of a meningococcal disease outbreak is difficult to assess, the Advisory Committee on Immunization Practices (ACIP) has developed recommendations for the evaluation and management of outbreaks of meningococccal disease. These recommendations are based on experience with serogroup C meningococcal disease outbreaks in the U.S. and may be applied to other vaccine-preventable meningococcal serogroups (A, Y, and W-135).

Vaccination of the population-at-risk may be recommended in the event of an organization- or community-based outbreak. Definitions of these outbreaks follow:

**Organization-based outbreak:** the occurrence of three or more confirmed or probable cases within 3 months in persons with a common affiliation but who were not close contacts of each other, resulting in a primary disease attack rate of at least 10 cases per 100,000 persons.

**Community-based outbreak:** the occurrence of three or more confirmed or probable cases within 3 months in persons living in the same area who were not close contacts of each other and who do not share a common affiliation, with a primary attack rate of at least 10 cases per 100,000 persons.

A detailed description of the ACIP recommendations including definitions and the formula for calculating the attack rate in a population may be found in the ACIP statement: *MMWR,* Control and Prevention of Meningococcal Disease and Control and Prevention of Serogroup C Meningococcal Disease: Evaluation and Management of Outbreaks, February 14, 1997, Vol. 46, No. RR-5.